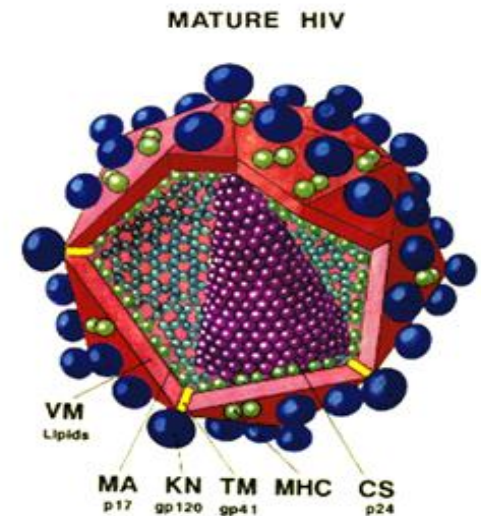
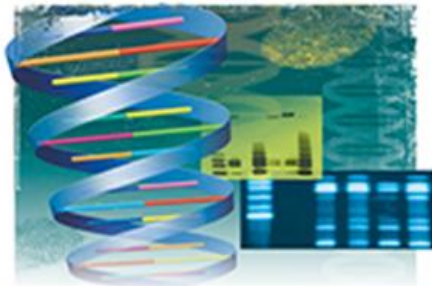


AIDS & IMMUNOLOGY

By

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Aim & Objectives

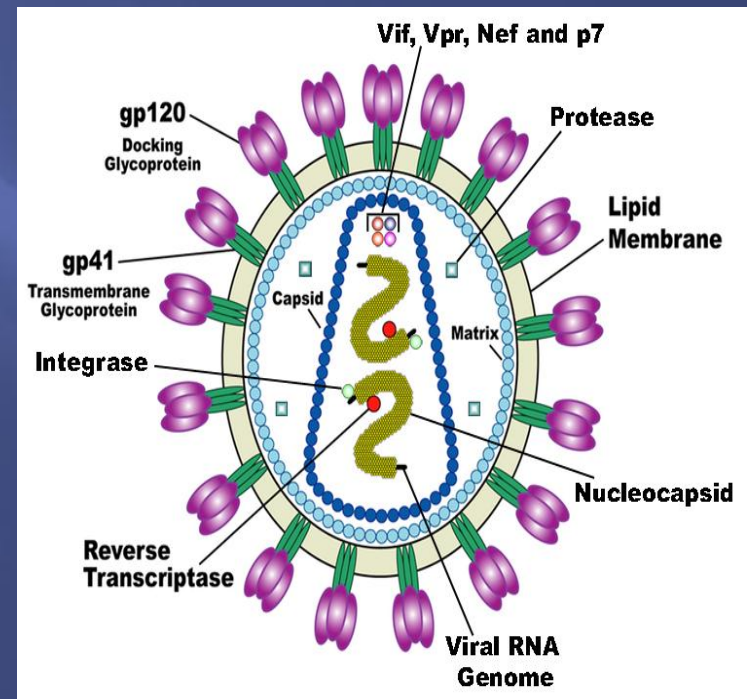
- The aim of this lecture is to introduce the basic facts about the virology and immunology of the human immunodeficiency virus(HIV).

Objectives:

- - Discuss the structure of HIV and understand its life cycle
- - Understand how it causes systemic infection.
- - know the viral dynamics & the route of transmissions.
- - Understand the immunological evolution and the immune response in HIV-infected patients.
- - Explain the immunological basis of HIV immune deficiency (immunopathogenesis) in adults and children.
- - Understand the mechanism and significance of HIV variability.
- Mangments of HIV.

HIV Virion

- HIV is different in structure from other retroviruses.
- Spherical; diameter about 120 nm, around 60 times smaller than a red blood cell
- composed of two copies of positive single-stranded RNA.
- surrounded by the viral envelope.
- The RNA genome consists of at least seven structural landmarks ([LTR](#), [TAR](#), [RRE](#), PE, SLIP, CRS, and INS).
- Nine genes (*gag*, *pol*, and *env*, *tat*, *rev*, *nef*, *vif*, *vpr*, *vpu* encoding 19 proteins.



HIV virus types:

➤ HIV-1:

- Causes HIV infection worldwide.
- Highly virulent.
- Highly susceptible to mutations.

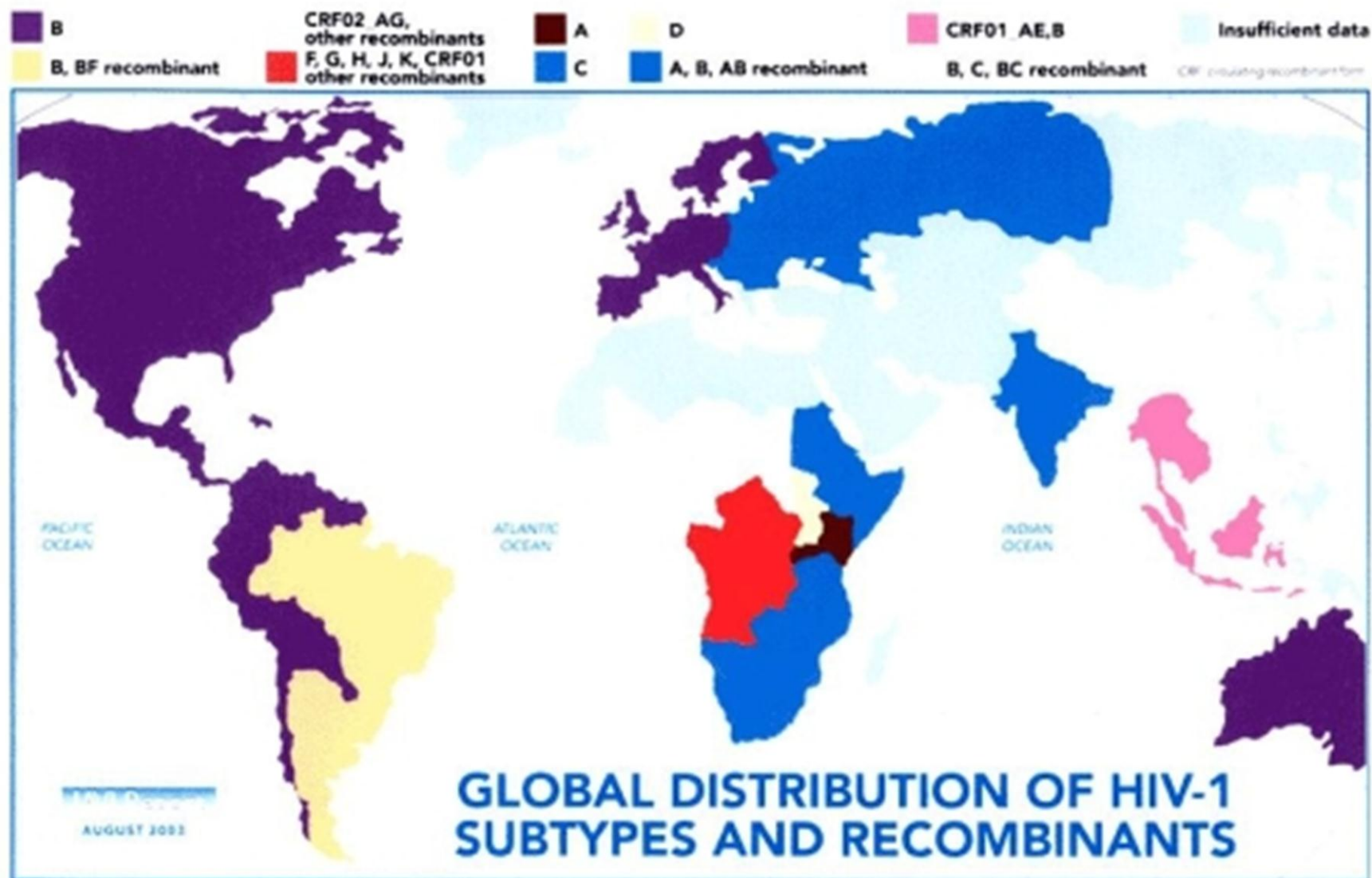
➤ HIV-2:

- Causes the infection in specific regions e.g. West Africa
- Relatively less virulent.
- Relatively less susceptible to mutations.

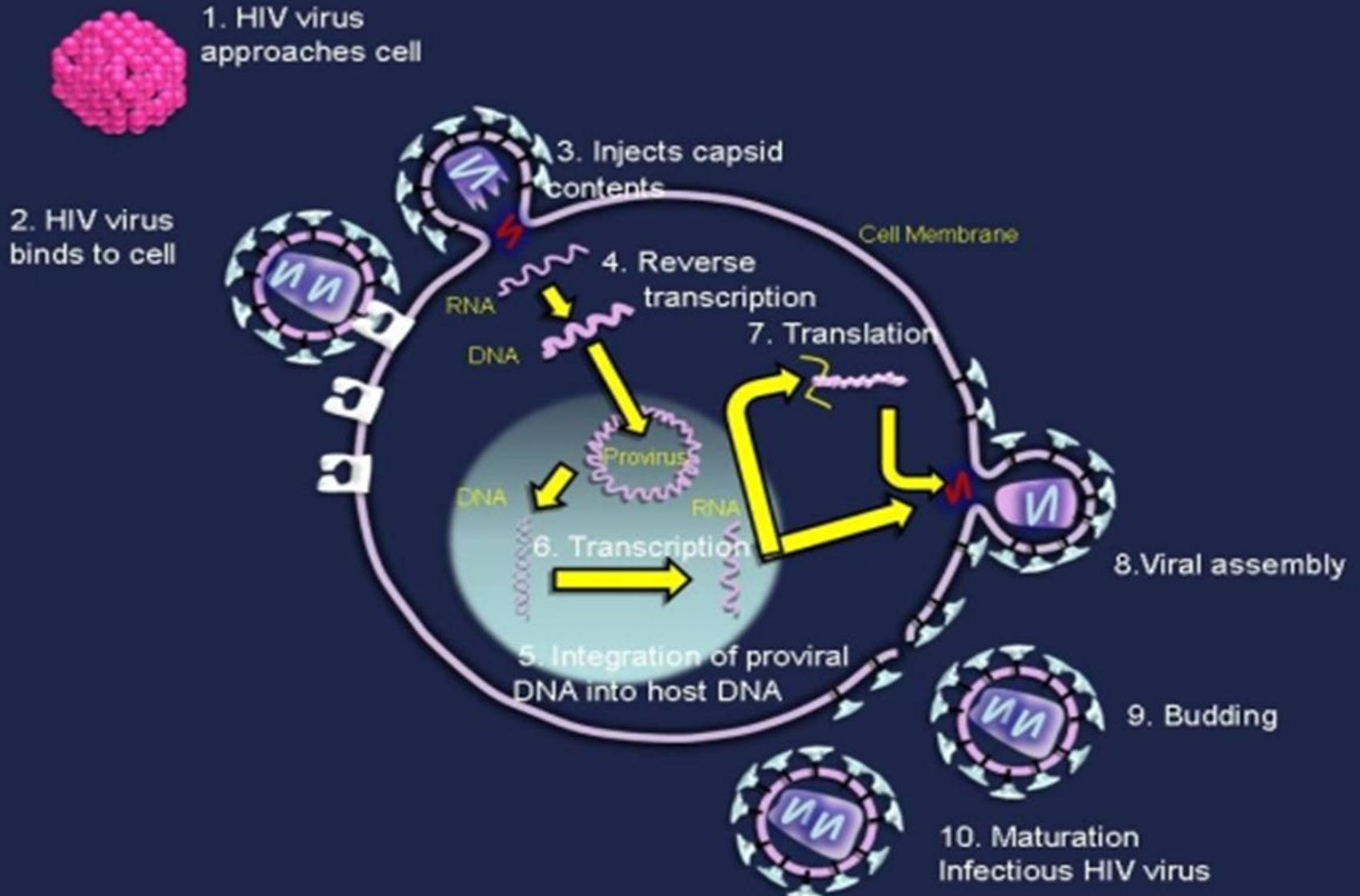
HIV subtypes in the world:

- Infection with HIV-2 causes slower disease progression and is more benign than infection with HIV-1.
- HIV-1 is further divided into **three groups**, group M (main group, >98%), group O (outlier, <1%), and group N (new, <1%).

- Group M is responsible for the majority of HIV-1 infections worldwide and can be further subdivided into recognized phylogenetic subtypes or **clades**:
- Subtype A: 23%; subtype B: 8%; subtype C: 56%; subtype D: 5%; subtype E: 5%; and subtypes F-K: 3%.
- There are also **recombinants**, which contain a mix of these subtypes.
- Common recombinants are mixtures of subtypes AE and AG; uncommon recombinants are mixtures of the subtypes AGHK, AFGHJK, AB, and BC.



HIV life cycle



Viral quasispecies

- A **viral quasispecies** is a group of viruses related by a similar mutation or mutations, competing within a highly mutagenic environment.
- Viral quasispecies can be considered as cases of coupled mutation-selection balance models for haploid organisms.

HIV variability

Quasi-species:

- In each patient, more than 10^9 new viruses are produced every day! During the replication process, the enzyme reverse transcriptase, which transcribes the RNA into DNA, has a high error rate: for each 10,000 nucleotide conversions of RNA into DNA, 1 error occurs.
- Because there are about 10^4 nucleotide positions/genome, this rate can lead to $10^4 \times 10^{-4} \times 10^9 = 10^9$ mutations per day.
- Each new generation of viruses is slightly different from the previous ones, and this constant evolution helps HIV remain one step ahead of the immune system.

Transmission of HIV :

Sexually:

The most common mode of HIV infection is **sexual transmission** at the genital mucosa through **direct contact** with infected blood, semen and vaginal secretion.

Parenterally:

- *Direct exposure to infected blood and blood products.

- *Use contaminated needles and syringes as in (drug abuser) and Tattooing.

- *Through contaminated **surgical** and **dental instruments.**

- *Sharing contaminated razors , tooth brushes, and nail cutters.

Transmission of HIV :

From mother to child

Infected mother transmit HIV to their babies transplacentally (vertical 25%) ,

but Treatment of the mother with antiretroviral Anti-reverse transcriptase (*Zidovudine*) during **pregnancy** can reduce transmission in most cases.

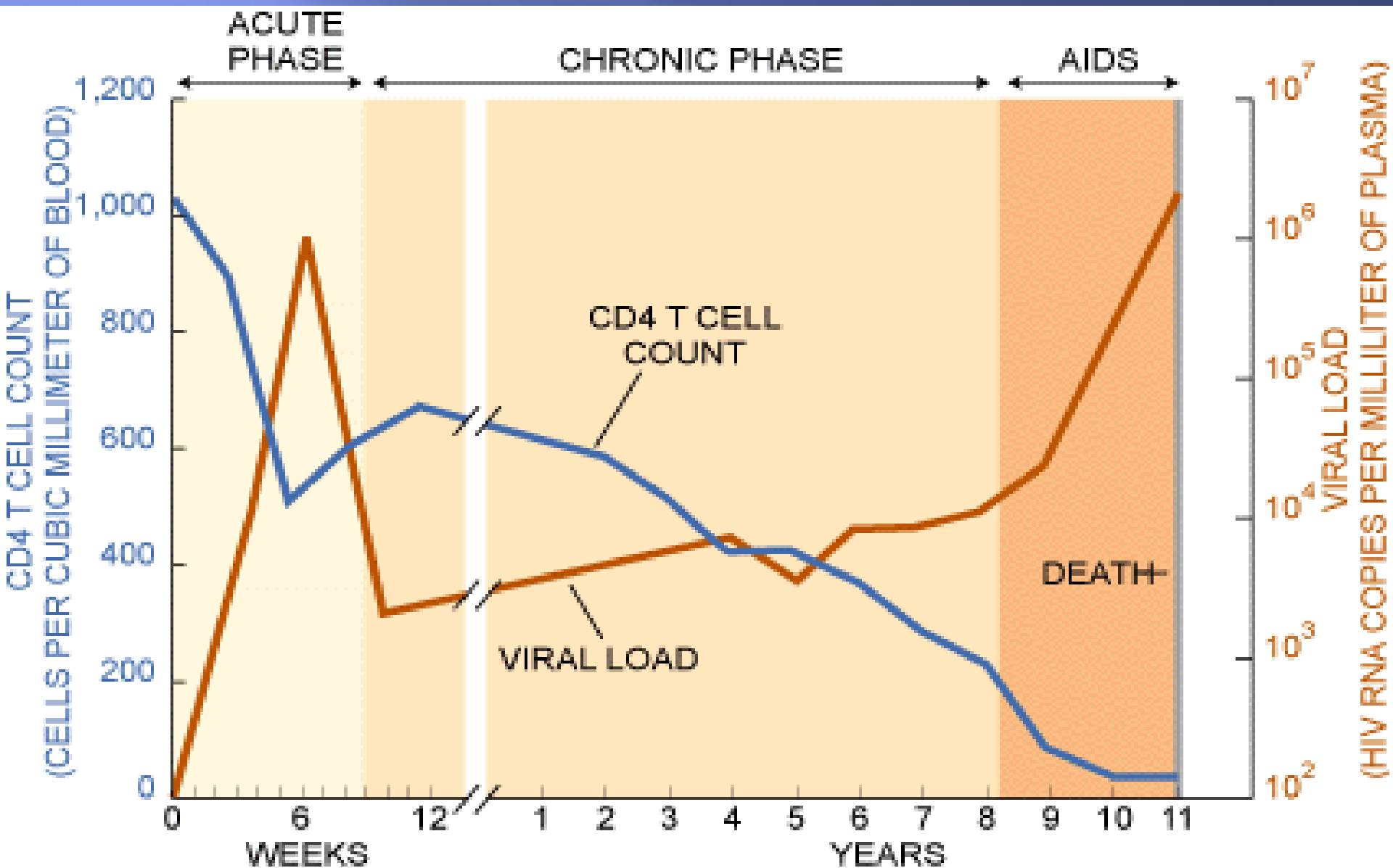
Transmission via Delivery

Virus spread to child perinatally mainly (50%) during delivery , given Anti-reverse transcriptase (Nevirapine) as single dose during delivery can reduce the transmission .

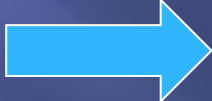
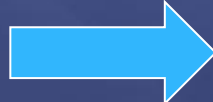
Breast feeding also an important way of perinatal transmission (25%).

Antiretroviral treatment of the mother and infant after birth can also significantly decrease the risk of HIV infection in the newborn.

Natural Course of HIV Infection



The Course of HIV-infection

- The course of HIV-infection can be divided into three stages:
 - The acute phase
 - The chronic phase  1- (PGL)
 2-(ARC)
 - **AIDS**

Acute phase:

- Incubation period (2-4 weeks) ,this phase Lasts for about 12 weeks.
- Rapid viral replication (high viral load RNA in the serum).
- Gradual decrease in CD4 cell count.
- 25-65% of patients develop symptoms resemble infectious mononucleosis or Flu like syndrome (**fever**, headache, anorexia, **fatigue**, lymphadenopathy , **myalgia** ,sore throat & skin rash).
- Some of patients may develop aseptic meningitis.
- About 13% to 40% of the patients will be **asymptomatic**.

Chronic phase:

- Lasts for about 10 to 15 yrs in adults, 5 years in children.
- Low viral load.
- CD4 count $> 500/\text{ml}$
- Totally asymptomatic but the patients **still contagious**, at the end of this stage patients start to develop PGL and ARC.

AIDS:

- The end stage of the disease.
- Continuous viral replication (high viral load viral RNA in the serum).
- Marked decrease in **CD4 cell count < 200**
- Persistent or frequent **multiple opportunistic infections** e.g. Pneumocystis pneumonia and development of unusual cancer (Kaposi sarcoma)

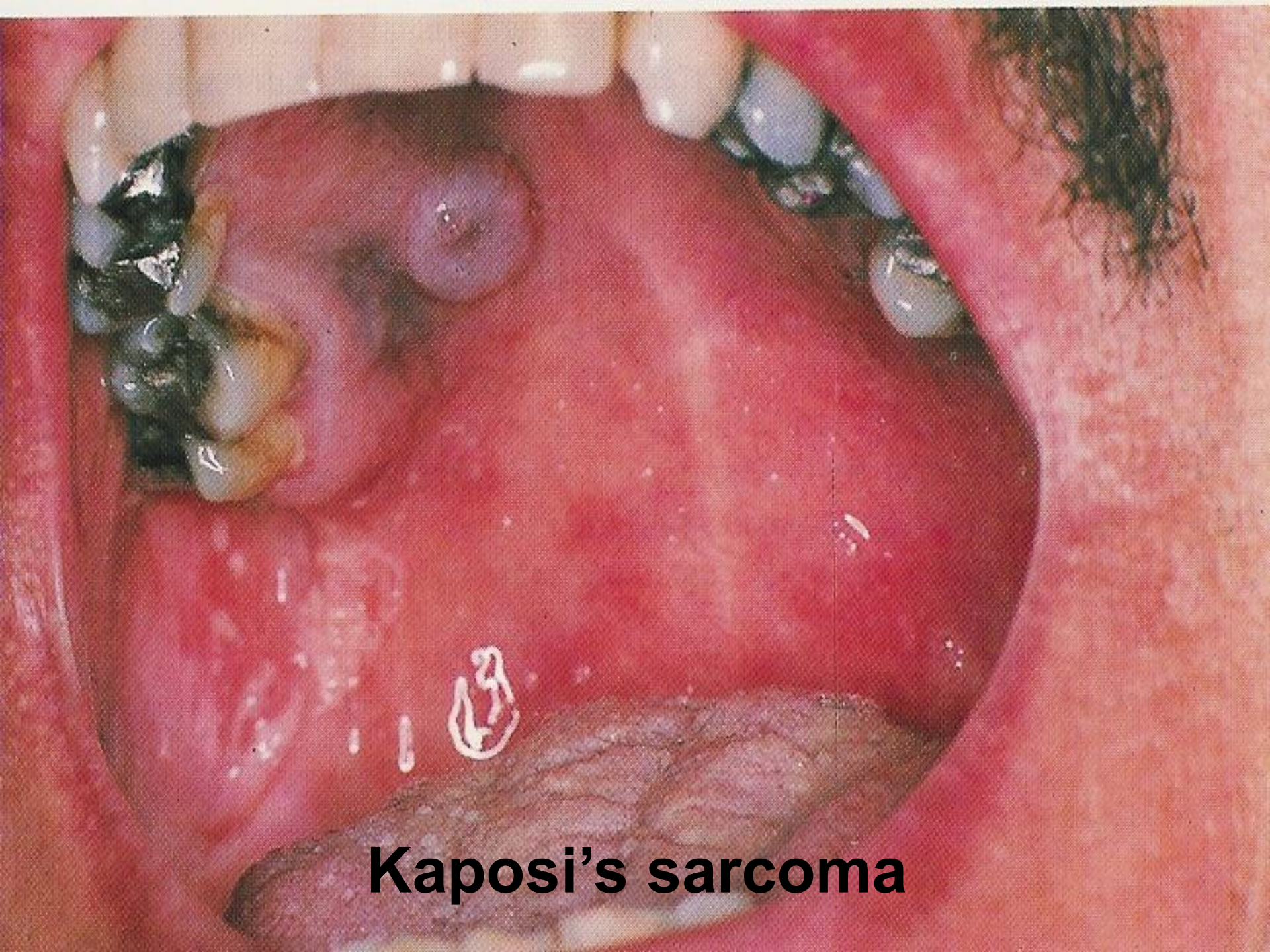


Kaposi's sarcoma

&



Slim disease



Kaposi's sarcoma

A-Persistent generalized lymphadenopathy (PGL)

Is defined as enlargement of lymph nodes for at least 1 cm in diameter, and must meet the following conditions:

- Persists for at least 3 months.
- In the absence of any illness or medication known to cause PGL.

B-AIDS-related complex (ARC)

Is a group of clinical symptoms that come before AIDS and may include the following:

- Fever of unknown origin that persists > 1 month.
- Chronic diarrhea, persisting > 1 month.
- Weight loss(Slim disease) > 10% of the original weight.
- Fatigue.
Neurological disease as myelopathies and peripheral neuropathy.

How to diagnose an HIV patient?

- Patient's history with or without clinical symptoms may give hints for a physician whether the patient has ever exposed to HIV or not.
- Screening patient's serum by **ELISA**; if the result is +ve we repeated the specimen twice in duplicate if still giving **+ve** result will do confirmatory tests (**Western Blot**).
- Blood viral load by PCR is also used as confirmatory test and to follow up patients response to treatment.

Diagnosis of an HIV infection

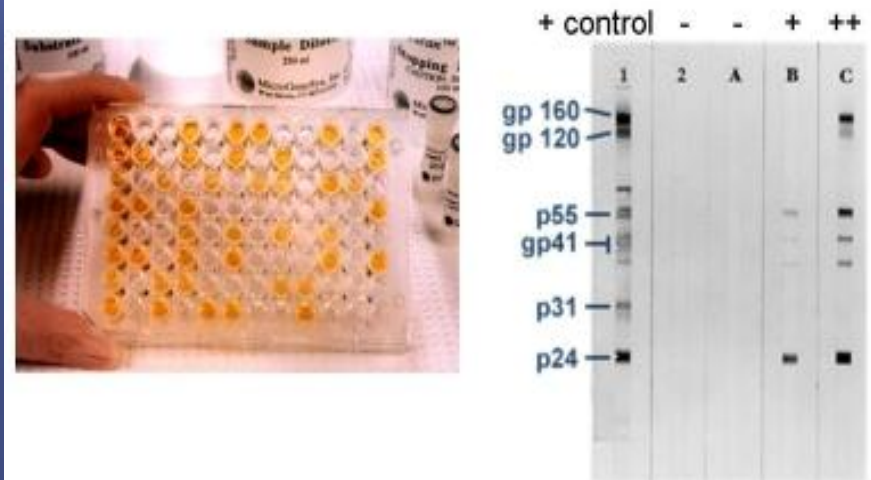
Testing for antibodies in the peripheral blood (or in oral fluids).

Antibodies are unlikely to be detected until 6 weeks after infection in the majority of cases, and a small proportion of people (<1%) take up to 6 months to develop antibodies.

There are different HIV antibody tests available, such as:

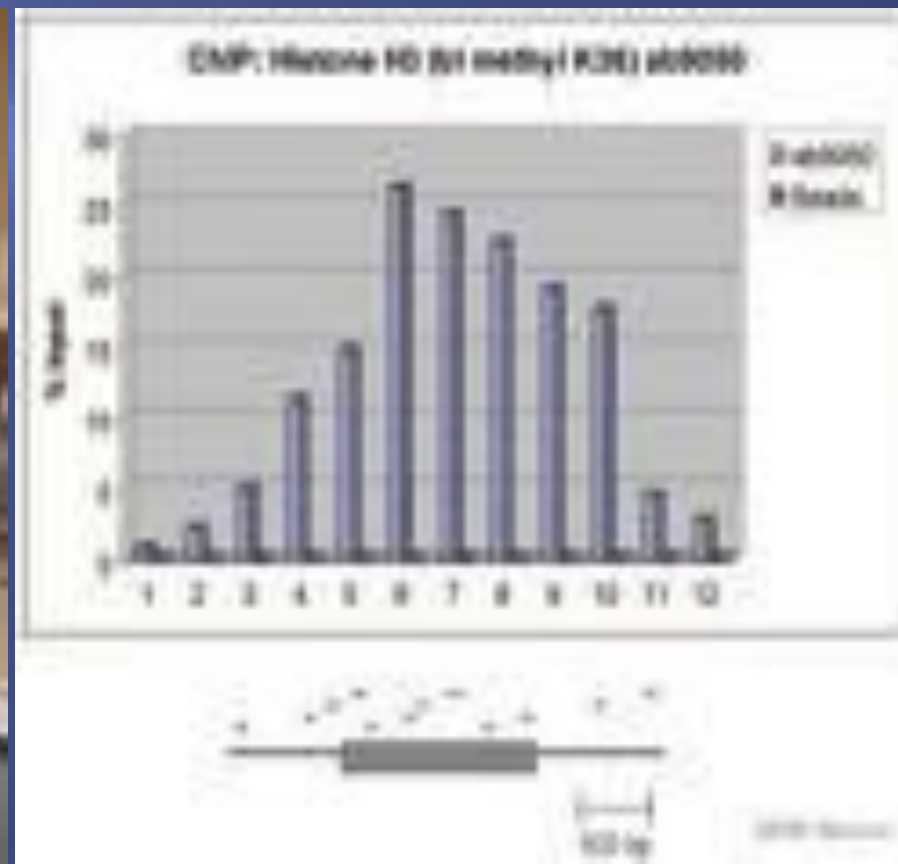
- Enzyme-linked immunosorbent assay (ELISA), high sensitivity, used in laboratories
- - Rapid tests can be used in all settings and offer fast results.
- - Western blot, high specificity, used as an HIV confirmation test

ELISA Serodiagnosis and first generation HIV confirmation test: western blot



PCR

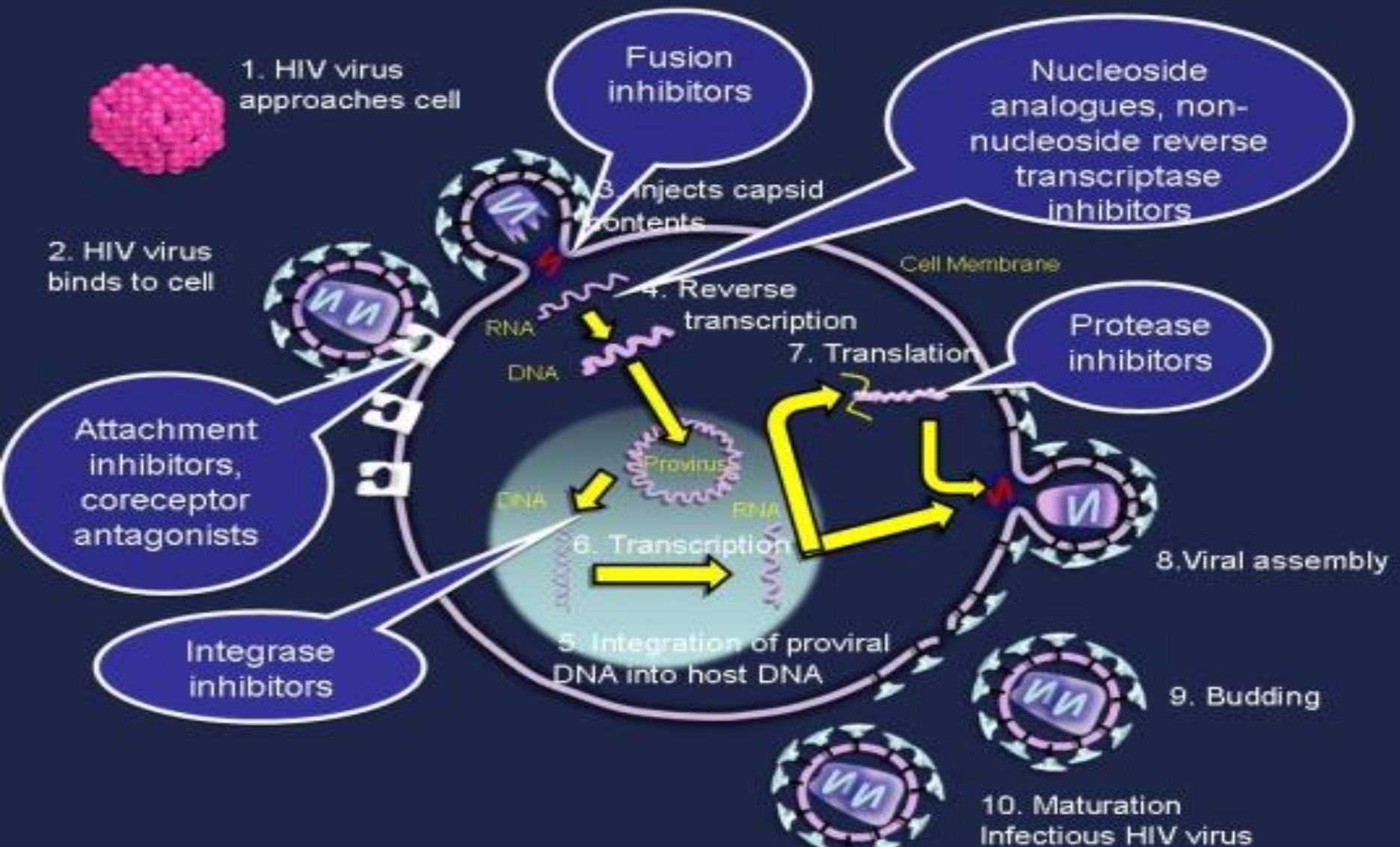
For detection of **HIV RNA** in the blood (viral load) this test is important for HIV diagnosis in infant of infected mother and also to monitor the antiviral treatment



Treatment

- Is a combined therapy known as high active antiretroviral therapy (HAART).
- **NOTE:** HAART does not clear the virus, and should be taken all life.
- **NOTE:** HAART treated patients are still contagious even if their blood viral load below detection (< 50 copies/ μL).
- HAART is usually composed of two reverse transcriptase inhibitors and one protease inhibitor.

Possible interactions of drugs with the virus life cycle:



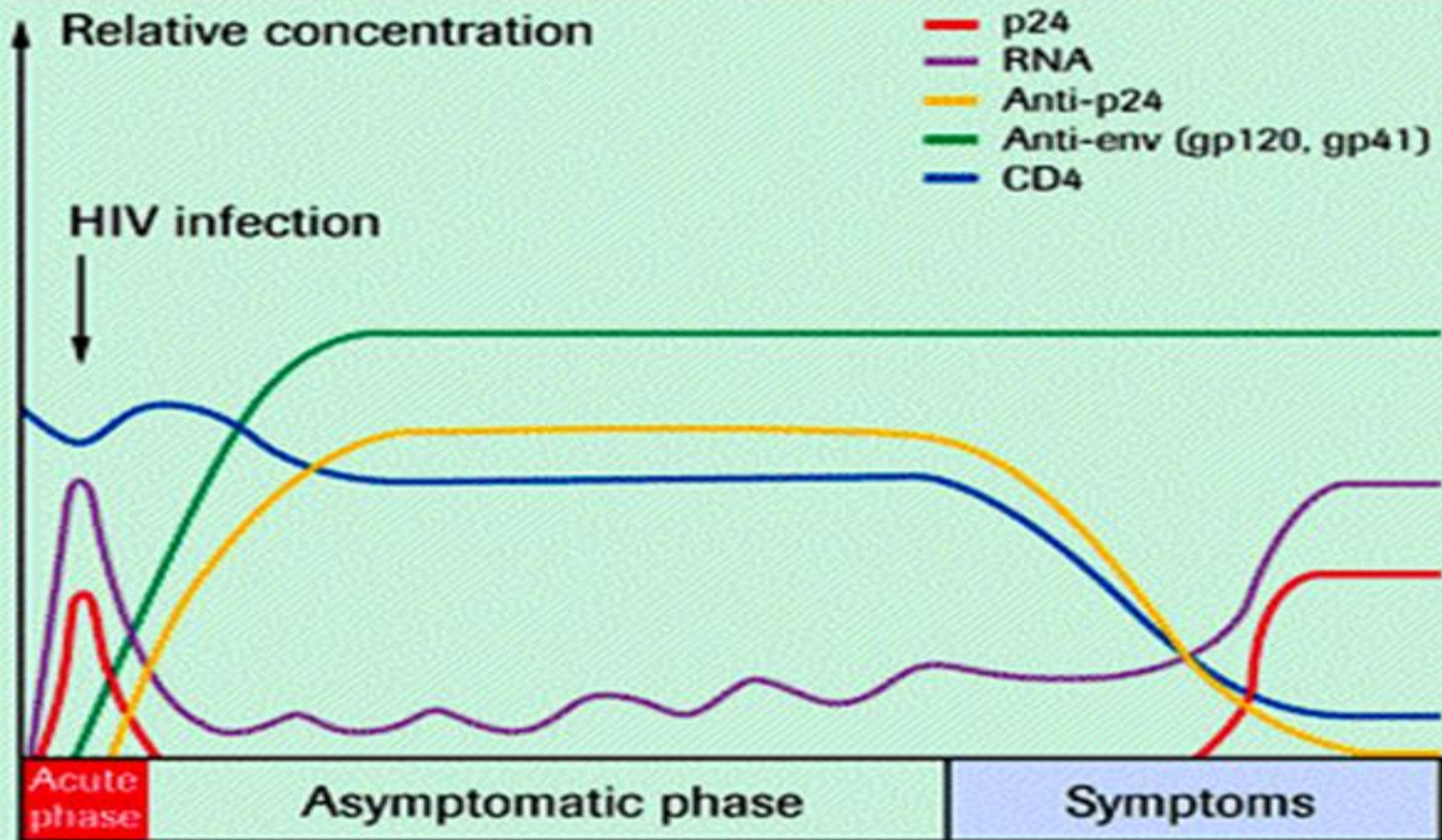
Prevention & Control:

- **There is no vaccine available yet for HIV**
- Practice safer sex .
- Do not share razors, tooth brushes, etc
- Do not share needles and syringes
- Avoid direct exposure to body fluids
- Educate the public about HIV-infection.

Immune Response to HIV Infection

- Immunology: humoral vs. cell-mediated.
- HIV biology: complex series of events leading to viral entry and course of infection; evasion of immune system.
- Immune response to HIV: weak humoral response, strong cell-mediated response diminished over time by depletion of helper T-cells

Serological profile of HIV infection

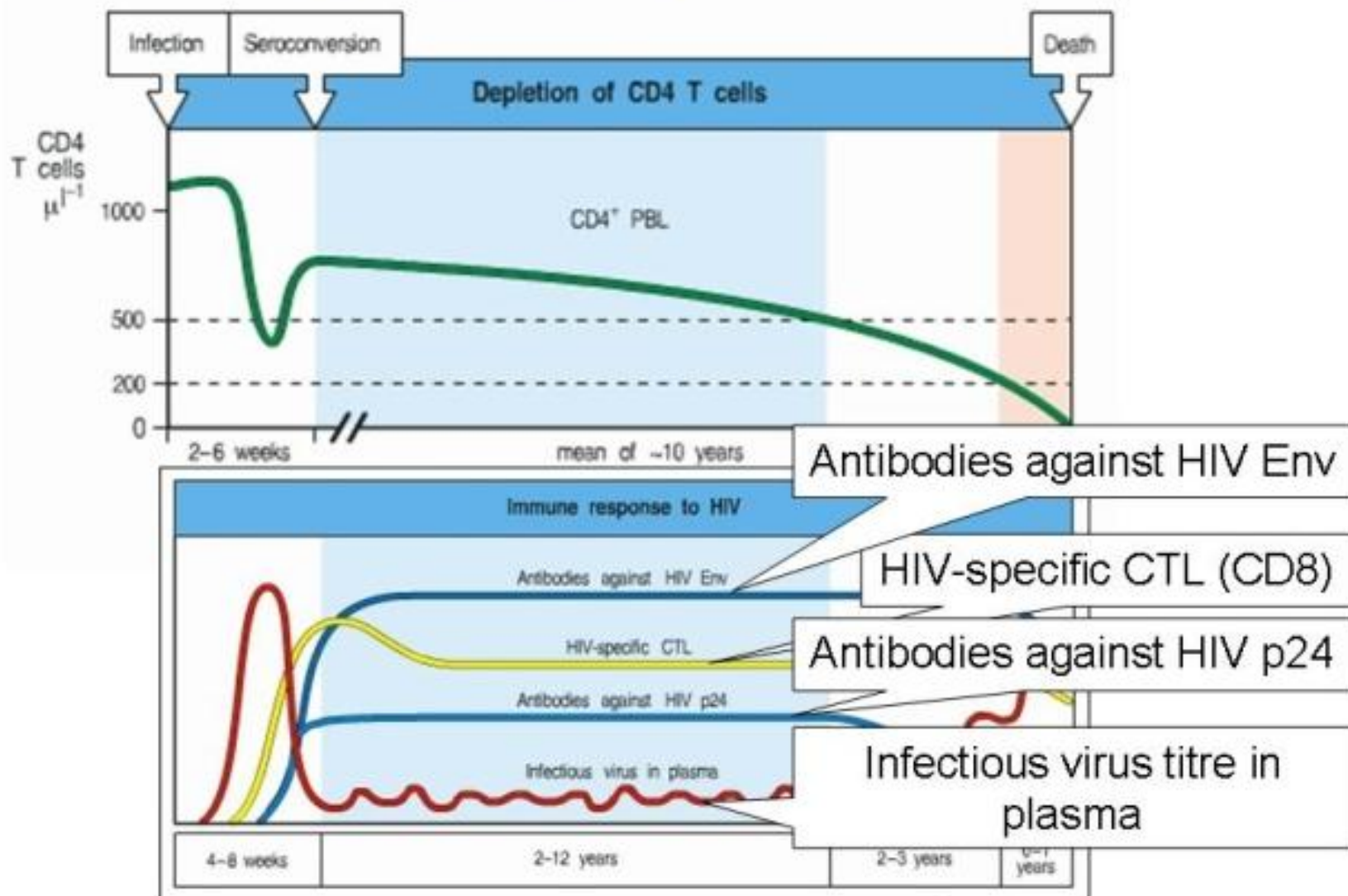


Immune responses to HIV infection

- Most people infected with HIV → effective immune response to the virus during the first few months of infection.
- The responses come in two forms: **cellular and humoral**.
- The cellular response refers to the activity of the CD4 and CD8 T cells, the latter known as cytotoxic lymphocytes.
- The humoral response refers to antibody production and activity CD8 T cells act against HIV in two different ways during primary infection:
 - - by directly killing HIV-infected cells
 - - by secreting anti-HIV molecules such as chemokines.

- In most HIV infected people, CD8 T cell counts fall again after infection, some people continue to exhibit strong HIV-specific CD8 T cell responses which control viral load.
- CD8 T cells play a crucial role in determining the speed of HIV disease progression.
- **CD4/CD8 cell ratio:** To obtain a better picture of disease progression, it is advisable to measure the CD4/CD8 cell ratio.
- The normal ratio is about 1 to 1.5.
- If the disease is progressing, CD4 will decline and CD8 will stay the same or increase and the CD4/CD8 ratio will be <1 , indicating disease progression.

The loss of CD4+ T cells eventually creates immune deficiency and inability to control HIV



Test Your Self

- Discuss the route of transmission of HIV horizontal & vertical bases on phases??.
- Differentiate between the different types of HIV worldwide??
- Discuss the possible interactions of drugs with the virus life cycle??.
- Discuss the viral quasispecies??

Study resources

- Mim's Medical microbiology WW.CDC.gov.
- Medscape.com.
- WHO.int.org.

THANK YOU

• Questions?

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